Nippon Yakurigaku Zasshi. Japanese Journal Of Pharmacology
Volume 103, Issue 5 , May 1994, Pages 231-239
ISSN: 0015-5691

Effect of efonidipine hydrochloride (NZ-105), a new dihydropyridine calcium antagonist, on the experimental atherosclerosis in cholesterol-fed rabbits

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Abstract

We studied the effect of **efonidipine** hydrochloride [NZ-105:(+-)-2-[benzyl(phenyl)amino] ethyl 1,4-dihydro-2,6-dimethyl-5- (5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl)-4-(3-nitrophenyl)-3-pyridine-carboxylate hydrochloride ethanol], a newly synthesized dihydropyridine calcium antagonist, on atherosclerosis in 1% **cholesterol**-fed rabbits. NZ-105 (10, 30 and 100 mg/kg) was orally administered to the animals twice a day for 10 weeks. NZ-105 did not cause any significant change in the plasma lipid levels. The area of atherosclerotic lesion was reduced by 37% ($P < 0.05$) in the aortic arch and by 54% ($P > 0.05$) in the thoracic aorta of rabbits administrated 100 mg/kg of NZ-105. The content of **cholesterol** ester in the aorta was also reduced by 64% ($P < 0.05$) in the aortic arch and by 73% ($P > 0.05$) in the thoracic aorta. These results suggest that NZ-105 may suppress the development of atherosclerosis without affecting the plasma lipids. [Journal Article; In Japanese; Japan]

CAS Registry Numbers: **Cholesterol,** Dietary; Dihydropyridines; Lipids; Nitrophenols; Organophosphorus Compounds; 111011-53-1, **efonidipine;** 57-88-5, **Cholesterol;** 7440-70-2, Calcium

Citation Subset Indicators: Index Medicus

MeSH Terms: Animals; Aorta, chemistry (CH); Aortic Diseases, pathology (PA), prevention & control (PC); Arteriosclerosis, blood (BL), pathology (PA), * prevention & control (PC); Calcium, * antagonists & inhibitors (AI); **Cholesterol**, analysis (AN);

‹Cholesterol,› Dietary; Diet, Atherogenic; Dihydropyridines, * pharmacology (PD); English Abstract; Lipids, blood (BL); * Nitrophenols; Organophosphorus Compounds, * pharmacology (PD); Rabbits

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Japanese Journal Of Pharmacology
Volume 69, Issue 2 , October 1995, Pages 101-109
ISSN: 0021-5198

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Effects of efonidipine hydrochloride on cholesterol esterification mediated by beta-very low density lipoprotein in J774 macrophages

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Abstract

The effects of efonidipine hydrochloride (efonidipine), a dihydropyridine calcium antagonist, on the cholesterol ester metabolism induced by beta-migrating very low density lipoprotein (beta-VLDL) in J774 macrophages were studied. The cholesteryl ester content in the macrophages was increased by incubation with beta-VLDL, and the increase was inhibited by efonidipine. Oleic acid incorporation into cellular cholesteryl ester was increased by beta-VLDL in J774 macrophages. The incorporation at an early phase of beta-VLDL induction (0-3 hr) was inhibited by efonidipine. This inhibitory effect of efonidipine was greater at an early phase of beta-VLDL induction (0-3 hr) than at a late phase of the induction (8-11 hr). Pretreatment of the cells with efonidipine enhanced the inhibitory effect. Efonidipine also inhibited beta-VLDL degradation but not the binding and association in macrophages without pretreatment. beta-VLDL binding and association to macrophages were decreased by pretreatment of the cells with efonidipine. beta-VLDL metabolism was also decreased by dibutyryl cyclic AMP pretreatment. The decrease of beta-VLDL metabolism by efonidipine was prevented by co-treatment with efonidipine and HA1004, a protein kinase A inhibitor. Furthermore, efonidipine increased the intracellular cyclic AMP content in J774 macrophages. These findings suggest that efonidipine suppresses cholesterol ester deposition in atherosclerotic foam cells by inhibiting the modified lipoprotein metabolism and cholesterol esterification mainly through elevation of the cellular cyclic AMP level. [Journal Article; In English; Japan]

CAS Registry Numbers: Calcium Channel Blockers; Dihydropyridines; Lipoproteins, VLDL; Nitrophenols; Organophosphorus Compounds; 111011-53-1, efonidipine; 55985-

32-5, Nicardipine; 57-88-5, ◂Cholesterol;▸ 60-92-4, Cyclic AMP

Citation Subset Indicators: Index Medicus

MeSH Terms: Animals; Binding, Competitive; Calcium Channel Blockers, * pharmacology (PD); ◂Cholesterol▸, * metabolism (ME); Cyclic AMP, metabolism (ME); Dihydropyridines, * pharmacology (PD); Dose-Response Relationship, Drug; Esterification; Lipoproteins, VLDL, * metabolism (ME); Macrophages, * drug effects (DE); Mice; Nicardipine, pharmacology (PD); * Nitrophenols; Organophosphorus Compounds, * pharmacology (PD); Radioligand Assay

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Japanese Journal Of Pharmacology
Volume 69, Issue 2 , October 1995, Pages 101-109
ISSN: 0021-5198